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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/561,754

05/19/2006

Joel Slade

4-33247A

1611

1095

7590

06/08/2007

NOVARTIS

CORPORATE INTELLECTUAL PROPERTY

ONE HEALTH PLAZA 104/3

EAST HANOVER, NJ 07936-1080

EXAMINER

HAVLIN, ROBERT H

ART UNIT

PAPER NUMBER

1609

MAIL DATE

DELIVERY MODE

06/08/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.		Applicant(s)	
	10/561,754		SLADE ET AL.	
	Examiner		Art Unit	
	Robert Havlin		1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 December 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-14 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of the claims: Claims 1-14 are currently pending. The claims were amended at the time of filing, however, the amendments were not annotated in the amended version of the claims.

Priority: This application is a 371 of PCT/EP04/06915 (06/25/2004) which claims benefit of US 60/482,686 (06/26/2003).

IDS: No IDS was filed with this application.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1. Claims 1-14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 and 26-29 of copending Application No. 10/527628 and claims 6-11 and 20-35 of copending

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application 10/544919. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are methods of making the same compound using similar starting materials have a mere rearrangement of the method steps with obvious modifications of the reactants which are well known in the art, and the identical compounds are even taught in WO 02/102790.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

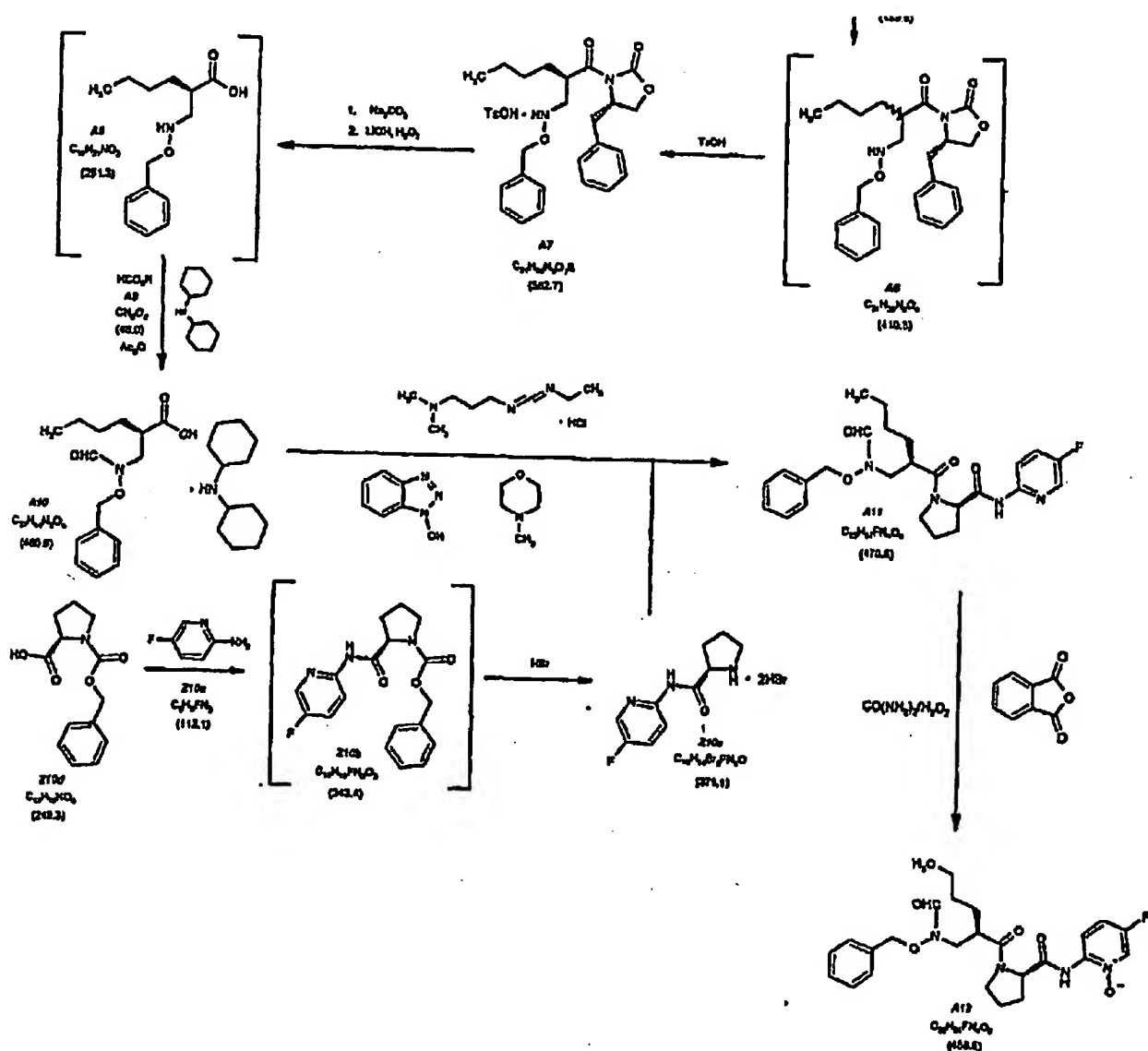
2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patel et al. (WO 02/102790) in view of Beckett et al. (US 6,503,897), Jacobs et al. (US 7,148,242), Fuhrer et al. (US 4,613,676), Shiraishi et al. (US 5,891,895), Goodman et al. (Biopolymers - Peptide Science, 2001, Vol. 60, p. 229-245), and Digenis et al. (J. Med. Chem. 1986, 29, 1468-1476).

The claims are drawn to a method of making a product with a process including the following:

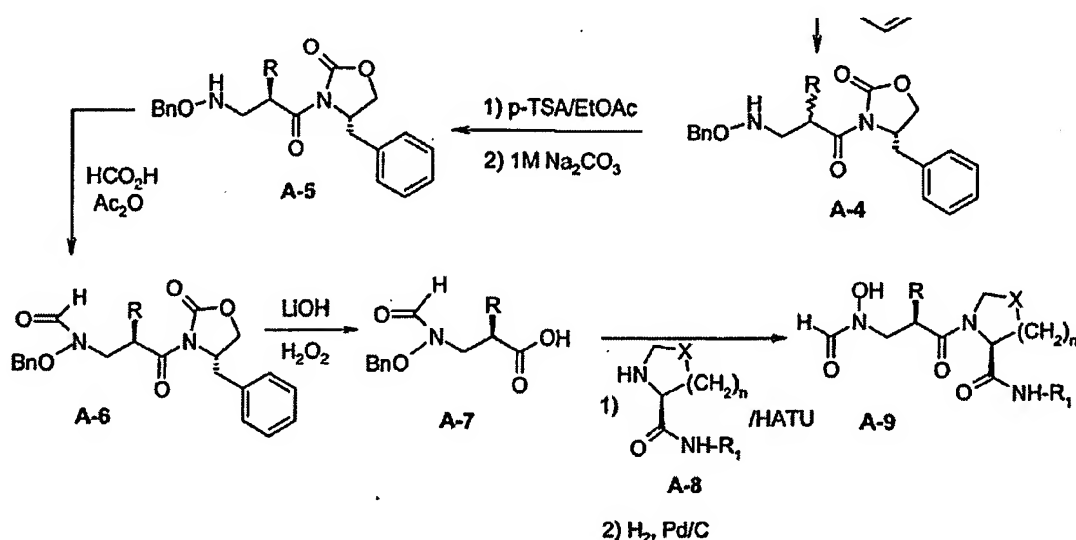
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Determination of the scope and content of the prior art

Patel et al. teaches a process for making a genus of compounds with several methods including the following:

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X = CH₂, -S-, -CH(OH)-, -CH(OR)-, -CH(SH)-, -CH(SR)-, -CF₂-, -C=N(OR)- or -CH(F)-; n = 0 to 3

The reference further teaches the oxidation of R1 and the deprotection of the hydroxyl in example 10 on page 24 (instant claims 2 and 3).

The reference teaches on page 19 (instant claim 4) [most relevant part **bolded**]:

*Example 1: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carbo-xylic acid pyridin-2-ylamide The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid A-7 (R=n-butyl) and pyrrolidine-2-carboxylic acid pyridin-2-ylamide A-8 (X = CH₂, n = 1, **Ri = 2-pyridyl**).*

The reference teaches on page 21 (instant claim 5):

*Example 5: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carbo-xylic acid- (5-fluoro-pyridin-2-yl)-amide The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid A-7 (R=n-butyl) and pyrrolidine-2-carboxylic acid (5-fluoro-pyridin-2-yl)-amide A-8 (X = CH₂, n = 1, **R, = 2- (5-fluoro) pyridyl**).*

The reference teaches on page 25 (instant claim 6):

Example 11 : 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carbo-xylic acid- (4-methyl-1-oxy-pyridin-2-yl)-amide The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid A-7 (R=n-butyl) and pyrrolidine-2-carboxylic acid (4-

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methyl-1-oxy-pyridin-2-yl)-amide A-8 [X = CH₂, n = 1, R, = 2- (4-methyl-1-oxy)-pyridyl].

The reference teaches on page 43 (instant claims 7 and 8):

Example 36: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid (5-fluoro-1-oxy-pyridin-2-yl)-amide The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid A-7 (R=n-butyl) and pyrrolidine-2-carboxylic acid (5-fluoro-pyridin-2-yl)-amide A-8 [X = CH₂, n = 1, R, = 2-(5-fluoro)-pyridyl] followed by the oxidation with MCPBA.

The reference teaches on page 16 (instant claims 9 and 10):

Step 3: 4-benzyl-3-[2-(benzyloxyamino-methyl)-hexanoyl]-oxazolidin-2-one (p-toluene-sulfonic acid salt) Compound A-3 (8.25 g, 28.7 mmol) is mixed with O-benzylhydroxylamine (7.07 g, 57.4 mmol, 2 equiv.) and stirred for 40 h at rt under nitrogen. The mixture is dissolved in EtOAc and p-TSA (21.84 g, 114.8 mmol, and 4 equiv.) is added to precipitate excess O-benzylhydroxylamine as a white solid. The white solid is filtered off, and the filtrate is concentrated to give a crude yellow oil (HPLC analysis indicated a small trace of starting material). Charging the crude yellow oil with excess diethyl ether and cooling to 0°C for 30 min gives a solid which is collected by filtration and dried in vacuo to afford the title compound as a white crystalline solid (single diastereomer).

...
Step 4: 4-benzyl-3-[2-(benzyloxyamino-methyl)-hexanoyl]-oxazolidin-2-one (A-5) To a solution of p-TSA (22.9 g, 39.3 mmol) dissolved in EtOAc (400 ml), is added 1M Na₂CO₃ (200 ml, 5 equiv.) and stirred at rt for 30 min. The layers are separated, and the aqueous layer extracted with EtOAc. The combined organic layers are dried over anhydrous Na₂SO₄, filtered, and concentrated to give the title compound as a pale opaque oil.

...
Step 5: N-[2-(4-benzyl-2-oxo-oxazolidine-3-carbonyl)-hexyl]-N-benzyloxy-formamide (A-6) A solution of compound A-5 (5.38 g, 13.1 mmol, 1 equiv.) in formic acid (7.4 ml, 196.6 mmol, 15 equiv.) is cooled to 0°C under nitrogen. In a separate flask, formic acid (7.4 ml, 196.6 mmol, 15 equiv.) is cooled to 0°C under nitrogen, and acetic anhydride (2.47 ml, 26.2 mmol, 2 equiv.) is added dropwise. The solution is stirred at 0°C for 15 min. The resulting mixed anhydride is slowly transferred via syringe into the original reaction vessel. The mixture is stirred at 0°C for 1 h, then at rt for 3 h. The mixture is concentrated, taken up in CH₂Cl₂, and washed successively with saturated NaHCO₃ and brine. The organic layer is dried over anhydrous Na₂SO₄, filtered, and concentrated to give an opaque oil which is purified by FC (hexane: EtOAc = 2 : 1 then CH₂Cl₂ : acetone = 9: 1) to yield the title compound as a colorless oil.

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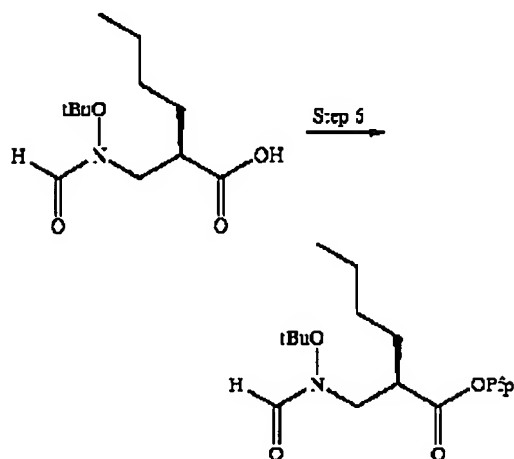
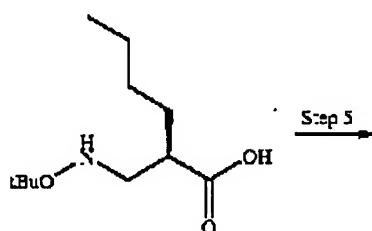
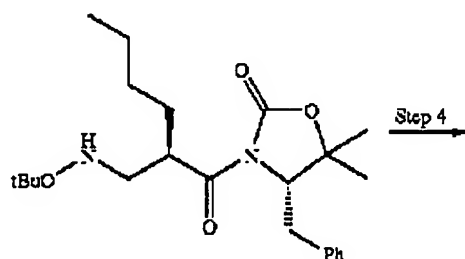
Step 6: 2- [(benzyloxy-formyl-amino)-methyl]-hexanoic acid (A-7) Compound A-6 (0.163 g, 0.372 mmol, 1 equiv.) is dissolved in THF (4.5 ml) and water (1.5 ml) and cooled to 0°C. Hydrogen peroxide (30% in water, 228 μ l, 2.23 mmol, 6 equiv.) is added dropwise followed by the slow addition of a solution of lithium hydroxide (0.019 g, 0.446 mmol, 1.2 equiv.) in water (350 μ l). The resulting mixture is stirred at 0°C for 1.5 h.

...

Beckett et al. teaches methods of making similar compounds and specifically on col. 15

teaches the method steps of (instant claims 11 and 12):

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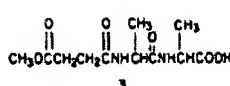
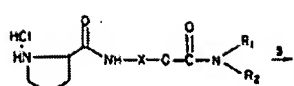


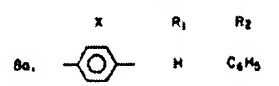
Reagents and conditions:

1. piperidine, HCHO , EtOH , 80°C , a.t.
2. tBuOOC- , Et_3N then 3-*thio*-4-*benzyl*-5,5-*dimethyl*-oxazolidin-2-one;
3. $\text{Et}_3\text{NOtBu.HCl}$, Et_3N , EtOH , 33°C , a.t.
4. LiOH , eq THF , 0°C , then 1M HCl .
5. HCOOH , Et_3N , CH_2Cl_2 ;
6. Pentachlorophenol, EDC , CH_2Cl_2

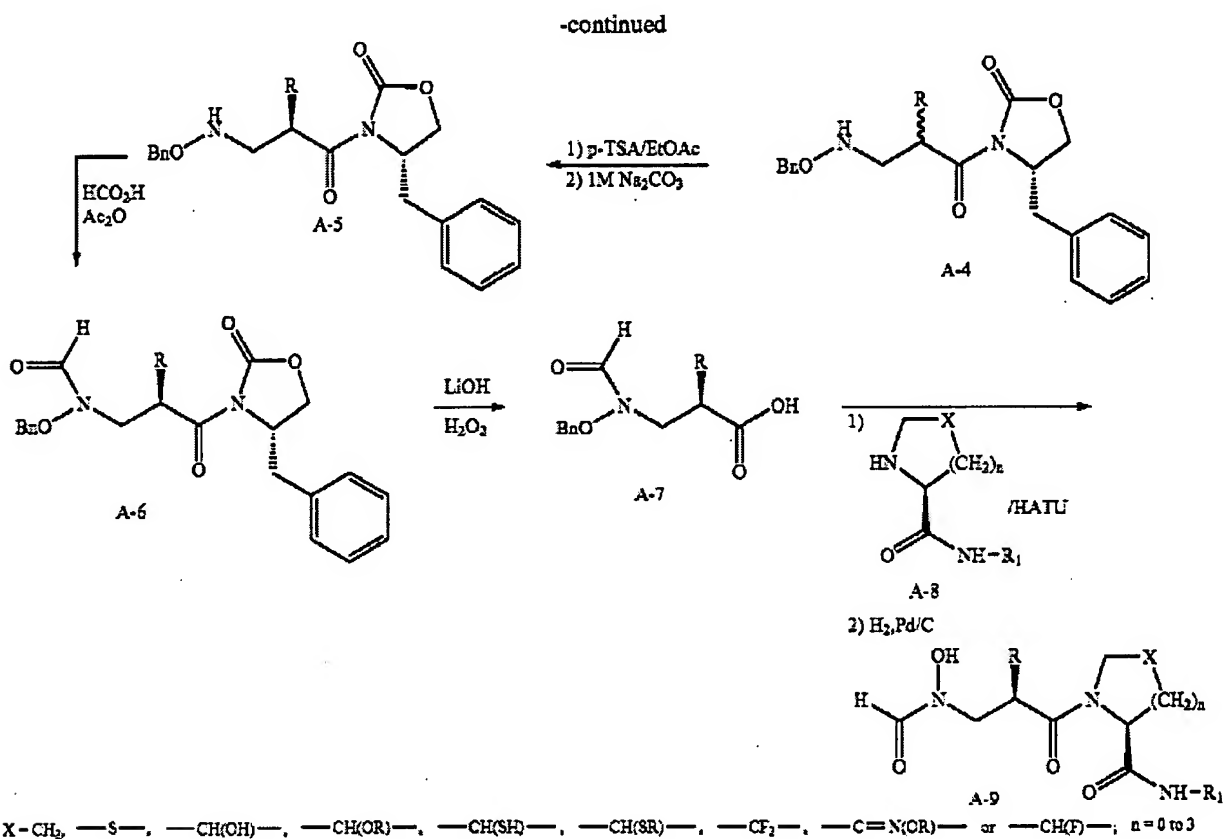
Fuhrer et al. teaches the use of dicyclohexylamine to precipitate carboxylic acid products with the motivation for the purposes of purification (instant claim 13).

Furthermore, the reference teaches the use of HOBt as a peptide activating agent.

Digenis et al. teaches the coupling of  and  to

give  in the presence of a coupling agent (N-methylmorpholine) on page 1473 and in scheme I (instant claim 14).

Jacobs et al. teaches another method of making the same product using the following:



Shiraishi et al. teaches the oxidation of pyridyl group into the oxy form with magnesium monoperoxyphthalate on col. 8, line 16.

Goodman et al. teaches the use of reagents for peptide coupling reactions, specifically EDC/HOBt (page 240, para. 1).

Differences between the prior art and the claims

The differences between the instant claims and the teachings of Patel et al. or Jacobs et al. amount to a rearrangement of the method steps and the utilization of different reagents. Specifically, the differences include the use of an amine or an alkaline metal hydroxide to form compound V (step 2B in claim 1 and claim 9) and the specification teaches the use of dicyclohexylamine. However, the use of dicyclohexylamine is well known in the art as a reagent for the precipitation of carboxylic acids such as peptides and Fuhrer et al. teaches its use.

Claim 9 also has the differences from Patel et al. of the reagents of EDC/HOBt in step 3 as a coupling agent and phthalic anhydride or magnesium monoperoxyphthalate in step 4 as an oxidizing agent. The use of EDC/HOBt is taught in Goodman et al. and the specific oxidizing agent is taught by Shiraishi et al.

Claim 14 teaches the coupling of the salt compound V with compound VI to give the compound VII with coupling agents. However, both Digenis et al. and Patel et al. teach the same coupling step without the "G" counter-ion of the salt. However, as described above, Fuhrer et al. teaches the use of dicyclohexylamine salts as reaction intermediates in coupling steps such as this one.

Finding of prima facie obviousness

As described above, the process claimed is nearly the same as that taught by Patel et al. with rearrangement of the method steps and the use of different reagents. Since the product produced by the methods are the same and the problem to be solved is the same, one of ordinary skill in the art would have been motivated to look to the teachings

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of Patel et al. and optimize the method using well-known reagents and rearrangement of method steps to arrive at the instant invention. Furthermore, it would have been routine for one of ordinary skill in the art to take the teachings of Patel et al. and the knowledge of organic synthetic methods as well as the teachings of the organic chemistry prior art references cited above to find a method of making the product with a higher yield.

Conclusion

All claims are rejected.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Havlin whose telephone number is (571) 272-9066. The examiner can normally be reached on Mon. - Fri., 7:30am-5pm EST.

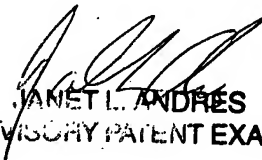
If attempts to reach the examiner by telephone are unsuccessful the examiner's supervisor, Cecilia Tsang can be reached at (571)-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Robert Havlin
Examiner

RH


JANET L. ANDRES
SUPERVISORY PATENT EXAMINER